The Gompertzian View: Norton Honored for Role in Establishing Cancer Treatment Approach

Larry Norton's multidimensional views of the world have come in handy for decades. As a child, he was rewarded by an art teacher for drawing objects from multiple vantage points. As a college student, he discovered a mistake in the tertiary structure of a chemical portrayed in a standard organic chemistry textbook. And as a clinical oncologist, he used mathematical models of tumor growth to create a new approach for treating breast cancer with drugs.

For this, Norton—now deputy physician-in-chief for breast cancer programs at Memorial Sloan-Kettering Cancer Center in New York—was awarded this year's David A. Karnofsky award, the highest honor given annually by the American Society of Clinical Oncology (ASCO). The award was sweet vindication for Norton and his efforts to advance an unpopular and poorly funded topic: the application of mathematical concepts to cancer biology.

Most scientists in this area have gone "underground," Norton said, to work through informal collaborations with little or no financial backing. Why? "Because biology and medicine tend to attract researchers who don't think in mathematical ways," explained Richard Simon, D.Sc., head of the National Cancer Institute's Biometric Research Branch and one of Norton's earliest collaborators. "There are exceptions, of course, but for the most part it's unusual for [cancer researchers] to put empirical observations into theories and then use those theories to develop testable hypotheses."

The Gompertzian View

Growing evidence suggests that mathematical models can provide key insights into tumor biology that can influence clinical trials in positive ways. Norton's own experience illustrates the point. During the mid-1990s, Norton proposed that clinical trials might incorporate the principles of Benjamin Gompertz, an 18th century mathematician. Gompertz is best known for his law of mortality, which holds that growth rates of populations are exponential at early stages of development and slower at later stages.

One hundred and fifty years later, Norton and Simon found that tumors follow Gompertzian growth functions—small tumors grow faster than larger ones. Moreover, the scientists found the rate of cell-killing by many drugs is proportional to tumor growth rates; that is, smaller tumors are more easily eradicated with drugs than larger tumors. From these observations, the scientists proposed the Norton–Simon hypothesis, which suggests that tumors given less time to regrow between treatments are more likely to be destroyed.

Dr. Larry Norton

The Norton–Simon hypothesis flew in the face of conventional views, which held that tumor growth is exponential and that chemotherapy kills in log intervals, meaning it kills constant fractions of tumor. When it was published in the 1970s, the hypothesis was met with such fierce hostility that Norton considered leaving oncology altogether. But years later, as head of the Cancer and Leukemia Group B (CALGB) Breast Committee, he oversaw the clinical trial that yielded results predicted by his hypothesis. In it, the intervals between chemotherapy treatments were shortened from three weeks to two, in accordance with the Gompertzian view that cell killing would be maximized if the tumor's regrowth was held in check. The treatment regimen, known as high-density dosing, improved survival among the trial's participants (*see* News, Vol. 95, No. 4, p. 254).

I Don't Work Weekends

The success of the CALGB trial showed that drug scheduling—in addition to timing and duration—is an important variable that must be investigated further. Yale School of Medicine professor Vincent DeVita, M.D., said the Norton–Simon hypothesis is "the greatest clinical trial innovation in 20 years."

"What Norton did was take information about biological growth and integrate it into treatment scheduling," DeVita said. "Ninety percent of clinical trials don't do that. We give chemotherapy on days one and eight and we give radiotherapy five days out of seven. Why? Because that's the schedule that conforms to a five-day work week. But frankly, tumors are smarter than that. We need to think about what's driving the growth of the tumor. And if that means giving the treatment at 2 a.m., then that's what we have to do."

Norton and his colleagues are now exploring additional applications for dose density, testing ever-shorter treatment intervals for cancers that include prostate and lung, in addition to breast cancer. The most applicable cases, Norton said, involve small tumors that grow rapidly and respond well to treatment.

But his acknowledged interests are going beyond clinical uses for the approach toward the molecular basis of the phenomenon itself. Norton's belief—one that he is exploring through collaborations—is that tumor tissue geometry plays a key role in

Gompertzian growth functions. According to his view, tissue geometry rivals cell behavior as the core determinant of both normal and malignant growth.

"Tumor growth rates aren't static," he explained. "They depend on the number of cells, how they are spatially arranged in space, and their relationships with the environment. This kind of geometry can be mathematically defined. It has to be determined by the protein and gene expression states at moments in time, which are predictable. We know there has to be a molecular basis for this phenomenon."

Tumors and Fractal Geometry

One way to study the geometric basis of the Norton–Simon curve, Norton proposed, is with fractals. In contrast to Euclidian geometry, which applies to objects with regular shapes, fractals describe irregular shapes, such as tumors and most other natural objects. The basic fractal unit is the "dimension," a noninteger value that describes the extent of complication in an irregular form.

Tumors have a higher fractal dimension than normal tissues—indicating their greater internal complexity. Norton noted that fractal dimensions have a tremendous buffering capacity, in that they grow in value even as the tumors themselves change little in terms of their apparent size. But once the dimension reaches a threshold value, the system changes radically, much as a ball traveling across a table drops when it reaches the edge.

"That's what happens with cancer," he explained. "People can go out and smoke and not have cancer and then suddenly they do. We're talking here about the power constants of the fractal dimensions—one incremental change gets them in trouble. Imagine if we understood the genes that control that power function. If we could understand those molecular changes, we might have a whole new target for intervention."

Fractal geometry already has a limited history in cancer research, where it is used to improve diagnosis and refine studies of tumor morphology. For instance, Rakesh Jain, Ph.D., professor
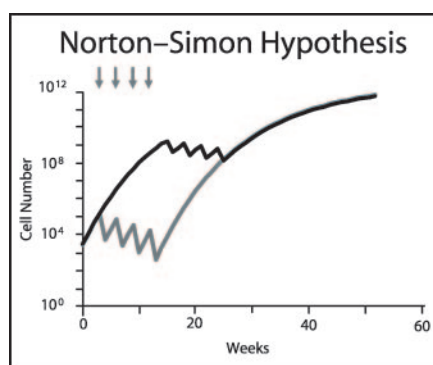
The Norton–Simon hypothesis states that the rate of tumor volume regression is proportional to the rate of growth.

of tumor biology at Harvard Medical School's Edwin L. Steele Laboratory, has used fractal analysis to measure random features of tumor circulatory anatomy. Tumor vasculature is highly abnormal, in part because excess endothelial cells contribute to poorly organized blood vessels. One of the effects of this chaos is to inhibit the uptake of therapeutic drugs into cancerous tissue.

Jain's use of fractal geometry led to a key insight, namely that, with anti-angiogenic drugs, scientists can lessen the chaos of a tumor's vasculature and improve the flow and efficiency of its blood supply. The "normalized" tumor vasculature may be more conducive to drug therapy, which could in turn be more effective in patients.

Multidisciplinary Ventures

Jain's work—similar to the cross-disciplinary approach that Norton has been advocating for years—incorporates his training in chemical engineering, a background that is unusual among cancer researchers. He said his interest in cancer was sparked 30 years ago by the late NCI pathologist Pietro Gullino, who encouraged him to model tumor perfusion with the some of the techniques he was using to model pollutants in the Delaware River. "I wrote the equations," Jain recalls of the exercise, "but the biggest problem was that there weren't any measurements for these parameters in the literature. There were no diffusion coefficients; it was a black box."

Over the years, quantitative measures for biological parameters have grown more common, but the disconnect

between mathematics and biology remains profound. Biology is, for the most part, a collection of empirical observations with little computational rigor. What's required, Simon suggests, is more multidisciplinary collaboration between the two fields. "People need to understand that computational biology is a full-fledged component of biology, not just a support function," he said. "It needs to be supported as an inherent part of how we move forward with cancer research."

Norton added that mathematics facilitates the convergence of biology, physics, chemistry, and other disciplines. With it, scientists can derive complete pictures of physiological processes, he said. Sometimes, while giving lectures, Norton evokes the profound simplicity of Newton's universal law of gravitation, or Einstein's theory of general relativity, noting these fundamental axioms gave rise to more complex rules that ultimately explain huge problems in physics and astronomy.

What these laws provide, he said, is the ability to describe phenomena that cannot be fully understood. "After all, what is gravity?" Norton asked. "Newton just described it mathematically; he didn't explain what it is in any conventional sense. I hope that when we have the biologic equivalent of Newton's laws we will better understand—and hence manage and prevent—cancer."

Norton acknowledged that the Karnofsky award has been a boon to his research. He's getting more calls for collaboration; he said he's appreciative to all those who stood by him.

Undoubtedly, clinical investigation is a challenging process that thrives on patience and luck. Norton got lucky. But if he hadn't, DeVita pointed out, the consequences could have been dire. "Let's say he pursued this and turned out to be incorrect," he said. "You can't turn around and go on to another 20-year project—you're too old. You get one shot like this. Larry was able to control the study and secure the financial support. He deserves to win prizes. Guys like him are an endangered species."

—Charles Schmidt